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BIOLOGICAL ACTIONS AND MECHANISMS UNDERPINNING THE ANTIUROLITHIATIC EFFECTIVENESS OF VARIOUS NATURAL HERBAL COMPOUNDS

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KEYWORDS:

Urolithiasis, ESWL, Recurrence, Herbal drug.

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ABSTRACT

Medicinal plants exist even before human being made their appearance on the earth. The raw materials for ayurvedic medicine were mostly obtained from plant sources in the form of crude drugs. The present day management of nephrolithiasis with open renal surgery is unusual and rarely used only since the introduction of Extracorporeal Shock Wave Lithotripsy (ESWL) which has almost become the standard procedure for eliminating kidney stones. However, in addition to the traumatic effect of shockwaves, persistent residue stone fragments and the possibility of infection suggests that ESWL may cause acute renal injury, a decrease in renal function and an increase in stone recurrence. The scientific documents reveal that the recurrence rate without preventive treatment is approximately 10% at 1 year, 33% at 5 year and 50% at 10 years suggesting its need. In light of this, exploitation of natural sources would be of much use. In the Indian traditional systems of medicine including Ayurveda, most of the remedies are derived from plants and their traditional applications are proved to be useful chiefly by decreasing the recurrence rate of urolithiasis without causing any potential side effects. Present review deals with treatment of urolithiasis with herbal drug involving various mechanisms of action.

INTRODUCTION:

Urolithiasis (from Greek *oûron*, "urine" and *lithos*, "stone") is the condition where urinary calculi are formed or located anywhere in the urinary system, or the process of formation of stones in the kidney, bladder, and ureters (urinary tract).[1] Calcium salts, uric acid, cystine, and struvite ($MgNH_4PO_4$) are the basic constituents of most kidney stones in the western hemisphere. Calcium oxalate and calcium phosphate stones make up 75–85% of the total and may be admixed in the same stone. Calcium phosphate in stones is usually hydroxyapatite [$Ca_5(PO_4)_3OH$] or, less commonly, brushite ($CaHPO_4H_2O$).[2]Urinary composition determines stone formation based on three factors: exceeding the formation product of stone forming components, the quantity of inhibitors (e.g., citrate, glycosaminoglycans etc.) and promoters (e.g., sodium, urates, etc.) in the urine[3]

S.No.	Promoters	Inhibitors	
		Inorganic	**Organic**
1	Calcium		
2	Sodium		
3	Oxalate	Magnesium	Nephrocalcin
4	Urate	Pyrophosphate	Tamm-Horsfall protein
5	Cystine	Citrate	Urinary prothrombin fragment
6	Low urine pH		Protease inhibitors
7	Tamm-Horsfall protein	Glycosaminoglycans	
			High urine flow

Table.1.Urinary stone promoter & inhibitors

Epidemiology-

Kidney stones occur one in 20 people at some time in their lives.Calcium stones are more common in men, the average age of onset is third to fourth decade(30-40year). Globally urolithiasis is the primary diagnosis for almost 2 million office visits, more than 600,000 emergency room visits, and more than 177,000 hospitalisations, totalling more than 2 billion dollars in annual expenditures according to survey of year 2000. In India, approximately 5 -7 million patients suffer from stone disease and at least 1/1000 of Indian population needs hospitalization due to kidney stone disease and the prevalence is increasing throughout the industrialized world[4]

Etiology-

The reasons why some people develop kidney stone are not fully understood. Aside from more obvious risk factor, metabolic condition e.g. hyperparathyroidism, cystinuria, hyperuricosuria, xanthiuria, hyperoxaluria& distal tubular acidosis are also common cause of stone formation.[5,6,7]

S.No.	Condition	Definition	Causes
1	Hypercalciurea >200mg/dl	Urinary calcium excretion Impaired renal calcium Absorption	Absorptive hypercalciurea Primary hyperparathyroidism
2	Hyperoxaluria >40mg/dl	Urinary oxalate excretion Excessive dietry intake	Genetic oxalate overproduction ↑ G.I absorption
3	Hypocitraturia <320mg/dl	Urinary citrate excretion Excretion	Impaired renal tubular acid Thiazide induced hypokalemia High animal protein diet High sodium intake
4	Hyperuricosuria >600mg/dl	Urinary acid excretion	Dietry protein excess
5	Hypomagnesuria < 50mg/dl	Urinary magnesium excretion	Limited intake of mg rich foods

Table.2. Major Cause of Calcium Stone Formation [8,9,10]

Pathogenesis-

Urolithiasis occurs as a consequence of the breakdown of a delicate balance to be maintained by the kidneys i.e. excretion of materials that have a low solubility and conservation of water[2]Kidney stones are classified according to their chemical composition. Crystallization and subsequent lithogenesis can happen with many solutes in the urine. Calcium oxalate (CaOx) is the predominant component of most stones accounting for more than 80% of stones. The remaining 20% are composed of struvite, cystine, uric acid, and other stones[8]

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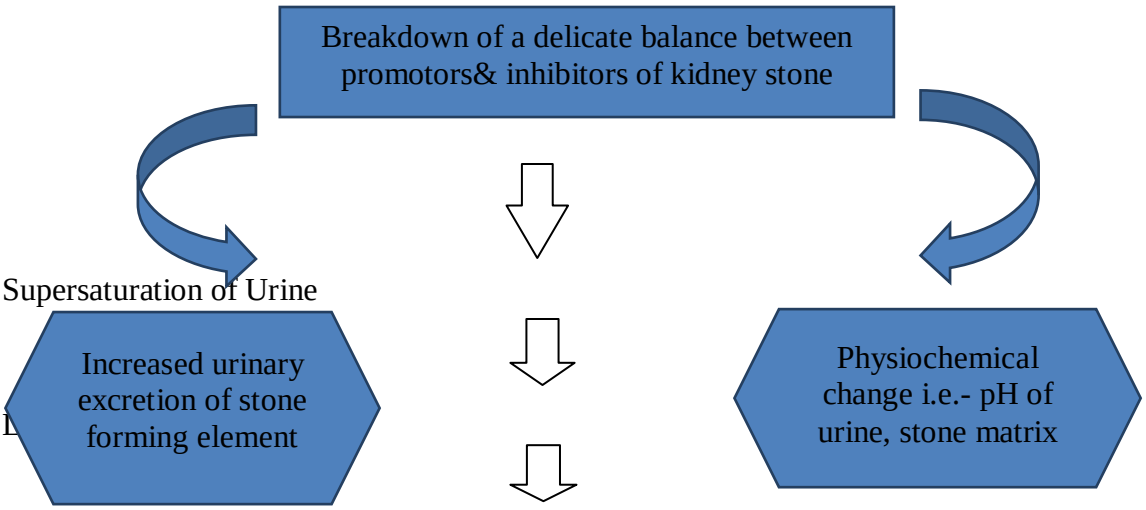

Fig.1. Pathophysiology of stone formation

Clinical signs and symptoms:

The clinical features of urinary tract stones are as follows:

S. No.	Stone Location	Common Symptoms
1	Kidney	Vague flank pain, hematuria
2	Proximal ureter	Renal colic, flank pain, upper abdominal pain
3	Middle section of ureter	Renal colic, anterior abdominal pain, flank pain
4	Distal ureter	Renal colic, dysuria, urinary frequency, anterior abdominal pain, flank pain

Table No.3.Relationship of stone location to symptoms[10]

Evaluation and treatment of patients with nephrolithiasis:

Adults with recurrent kidney stones and children with even a single kidney stone should be evaluated. A practical outpatient evaluation consists of two 24-h urine collections, with a corresponding blood sample; measurements of serum and urine calcium, uric acid, electrolytes, and creatinine, and urine pH, volume, oxalate, and citrate should be made. At least one urine collection should be made on a weekend when the patient is at home and another on a work day.[2,14]

The management of stones already present in the kidneys or urinary tract requires a combined medical and surgical approach.

S.No.	Stone Type	Treatment
1.	**Cystein**	Very high fluid intake (> 31/day) + oral alkali (urine pH >7.5) or D - penicillamine, a- mercaptopropionylglycine.
2.	**Uric acid**	High fluid intake (>2.5 l/day) + oral alkali (urine PH>6.2) or reduce purine intake or allopurinol (300mg)
3.	**Infected**	High fluid intake + antibiotic + cranberry juice (to ↓ PH < 6.2)
4.	**Calcium**	High fluid intake + relevant diatary advice and thiazide Diuretic: bebdroflumethizide (5 mg), chlorthalidone(25mg), potassium, citrate(1-2 × 30mEq/ day)
5.	**Xanthine**	Hereditary form: high fluid intake + oral alkali (urine PH > 7.4), latrogenic form: withdraw allopurinol.

Table.4: Medical method of prevention of urinary stone disease[1,15,16]

Surgical treatment like **(a)** Shock wave treatment which is the only non-invasive treatment for stone disease **(b)** Endoscopic management, both ureterenoscopic and percutaneous nephrolithotomy provides an efficient way to treat stones irrespective of anatomy, composition and burden.[17]. The severe nature of renal colic has promoted a lower threshold at which narcotic analgesic, thiazide like diuretic and potassium citrate is prescribed.

Herbal drugs in urolithiasis:

Medicinal plants have played a significant role in various ancient traditional systems of medication. Even today, plants provide a cheap source of drugs for majority of world's population. Several pharmacological investigations on the medicinal plants used in traditional antiurolithic therapy have revealed their therapeutic potential in the in vitro or in vivo models[6,18]. However, in addition to the traumatic effect of shockwaves, persistent residue stone fragments and the possibility of infection suggests that ESWL may cause acute renal injury, a decrease in renal function and an increase in stone recurrence. Most of the remedies are derived from plants and their traditional applications are proved

to be useful chiefly decreasing the recurrence rate of urolithiasis without causing any potential side effects.[19]There are various herbal drugs are available having different mechanism to treat urolithiasis.

Mechanism of action	Herbal drug	
Alteration in physiological pH	**Botanical Name**	**Common Name**
	Hypericumperforatum	St John's wort
	Bidenstripartita	three lobbed Begger
Diuretic activity	*Cerasusavium*	Cherry Stalk
	Celosia argentina	Wild cock comb
	Hygrophilaspinosa	*Kokilaksha*
	Cedrusdeodara	Devadar
	Urticadioica	Stinging nettle
	Cicutavirosa	*Cowbane*
	A uva-ursi	*Bearberry*
	Curculigoorchioides	Kali musli
	Digitalis purpurea	*Foxglove*
	Orthosiphonstemineus	*MisaiKucing*
	Convolvulus arvensis	Field Bindweed
	Raphanussativus	Radish
Antioxidant activity	*Citrus sinensis*	Orange
	Zingiberofficinalis	*Ginger*
	Mimusopselengi	Spanish cherry
	Hordeumvulgare	B*arley*
	Punicagranatum	*Pomegranate*
	Cymbopogoncitratus	*Lemon grass*
	Bergeniaciliata	Pigsqueak
	Curcuma longa	Turmeric
	Asphaltum Panjabinum	Shilajit
Inhibition of oxalate synthesizing enzyme	*Aervalanata*	Mountain knotgrass
	Tribulusterrestris	*Gokhru*
Mixed action	*C. anthelminticum*	Wormseed
	Phyla nodiflora	Frog fruit
	Mussaendaerythrophyla	Ashanti blood
	Citrus medica	*Citron*
	Stigma maydis	Corn Silk
	Tinospora cordifolia	Guduchi
	Trigonellafoenum graecum	*Fenugreek*

Table.5. List of herbal drug with their mechanism of action

1} Alteration of physiological pH:

The parameter urine pH is the leading factor that predominantly identifies the type of urine calculus. Crystalluria is pHdependent [20].At urine pH 5.0 and less the pure uric acid, inthe pH range from5.2 to 5.8 - the salts of uric acid, in the range from 5.0 to 6.0 – oxalates and in pH 7 - hydroxyl apatite are precipitated. Solubilisation of these calculi can be achieved by alteration of urinary pH.An increase in urinary pH might be responsible for dissolving complex of calcium &oxalate [21]. There are number of drug which act through this mechanism i.e.-

Hypericum perforatum-*Hypericum perforatum*, known as St John's wort, is a medicinal herb with antidepressant activity and potent anti-inflammatory properties. Hydroalcoholic extract of *Hypericumperforatum* leaves reduce Urine level of free calcium,phosphorous and the size and number of calcium oxalate deposits[22] besides diuretic effect, showed their effect on the urine pH and crystalluria. It had the capacity to increase urine pH, was diuretic of moderate action. It was interesting that urine pH after phytotherapy with extract of *Hypericum perforatum*L. was close to the level of healthy individuals.[23]*Hypericum perforatum*L. as monotherapy in the patients with urolithiasis is not rational due to presence of clinical complications.

Bidenstripartita-*Bidenstripartita* (LINN.)also known as three-lobed beggar belongs to the family Compositae. It mainly contain polyacetylenes, flavanoids, friedelane triterpenes and essential oils which may contribute to different therapeutic action of this herb.This plant was formerly valued for its diuretic and astringent properties, and was employed in fevers, gravel, stone and bladder and kidney troubles. The noted urine pH increase in prescription of *Bidenstripartita* L. did not change activity of stone formation process and the degree of crystalluria did not change.[23]

2} Diuretic activity:

Increasing urine volume decreases the saturation of salts & prevents precipitation of crystal at physiological pH. The type of fluids should be carefully selected to achieve the appropriate change of urine composition depending on stone composition.[14]All herbal medicine used for treatment of urolithiasis has diuretic action and some known to alkalize the urine[24] Synthetic diuretics like loop and thiazide cause inhibition of potassium secretion leading to potassium retention that has some toxic effects. On contrary, many herbs have been explored and found to possess potent diuretic activity with lesser toxic effects[25].Some herbal drug act through this mechanism are-

Cerasusavium- Wild cherry is a species of Prunus belongs to family Rosaseae. It has been used in hypertension, and in renal colic for analgesia due to its well-known diuretic effect. It contain sugars, organic acids and phenolic compound like-anthocyanins, flavan-3-ols and flavonol etc.It isfound that mean levels of urine calcium, sodium and chloride and urine volume were changed,but the amount of

urine potassium and urine osmolality did not change after administration of cherry stalk. Although no adverse reactionwas observed, soit should be used with caution in those with urolithiasisbecause of rising calcium excretion,[26]

***Celosia argentina*-**It is also known as wild cock's comb traditionally used as a diuretic. Triterpenoidsaponins isolated from the seeds of *C. argentea* and named as celosin E, celosin F, celosin G, and cristatain are responsible for its diuretic effect. It is reported that celosia seed extract at low & high dose decreases body wt, water intake, urine output, shift p^H to alkaline, prevent increase in urolithiatic promoter and decrease in urolithiaticinhibitor of kidney.It is concluded that it has a potent prophylactic effect on stone formation.[27]

***Hygrophilaspinosa*-**It is an erect and woody plant from the family Acanthaceae.The plant is used as demulcent, aphrodisiac, diuretic, urinary tonic and hepatoprotective substance. A literature survey revealed that *H.spinosa* is endowed with various chemical components such as alkaloids, phytosterols, mucilage and fixed oil etc. these constituent in aqueous extract may be the reason for antilithiatic activity againstethylene glycol induced lithiasis. Following ethylene glycol administration the excretion of calcium, oxalate, phosphate and protein were found to be increased in lithiatic group while in standard, curative and preventive groups these levels were significantly decreased ($P<0.01$). In conclusion, the plant *H.spinosa*has both prophylactic as well as curative property in urolithiasis ofrats.[28]

***Cedrusdeodara*-**Devadaris the plant of Pinaceae family having very good medicinal value. Ether extract (PECD) showed presence of volatile oils, triterpenes, saponins, phytosterols, fixed oils and due to which it produce diuretic and anti-urolithiatic activity without producing much hypokalemic effects. It has been observed that Concomitant administration of PECD for 10 days along with NaOx prevented elevated serum biochemical levels due to the elimination of these in urine.[29]

***Urticadioica*-** Stinging nettle is a herbaceous perennialflowering plant belongs to family Urticaceae. It mainly contain phytosterol, pentacyclintriterpenes, coumarins, ceramides and hydroxyl fatty acid. Although *Urticadioica* nettle has been used for treating several diseases, the main tradition for treatment of patients with kidney diseases is its use for urolithiasis. It is believed by some that this plant dissolves all stones in the body. It has been shown that continuous perfusion of aqueous extract of Urticadioica caused acute diuretic, natriuretic and hypotensive effects in rats which is responsible for its antiurolithiatic effect.[22]

***Cicutavirosa*-**Cowbane belongs to family Apiaceae. The oil of cowbane was found to be rich in sesquiterpenic compounds with β-farnesene (22.7%), α-humulene (5.4%), humulene epoxide II (5.9%), caryophyllene oxide (3.4%), germacrene D (3.2%) and α-farnesene (3.6%) as major

constituents. Diuretic and anti-urolithic activity ofaqueous extract of C. virosa may be due to its pseudoalkaloids content. These activity of *Cicutavirosa* are conformity to already report diuretic activity along with its specific effect on treating convulsions associated with dialysis in end-stage renal failure patients.(23)

A. uva-ursi-*Arctostaphylosuva-ursi*(bearberry) is a plant belongs to family Ericaceae. It exhibited pronounced diuretic and anti-urolithic activity may be due to the presence of arbutin, a phenolic glycoside along with ursolic acid,iso-quercetinand it has been reported by many researchers that A. uva- ursi could be effective in relieving pain associated with kidney stones, cystitis, nephritis as well as act as a diuretic(23)

Curculigoorchioides-Kali musli belongs to the family Hypoxidaceae. It consist of mucilage,phenolic glycosides, saponins and aliphatic compounds- cycloartane glycosides.Ethanolic root extract of *Curculigoorchioides* showed dose dependant diuretic activity. The diuretic property of the plant *Curculigoorchioides* favours antiurolithiaticactivity by hastening the process of dissolving or by flushing of the preformed stones. The possible mode of action of *Curculigoorchioides* may be due to excessive secretion or decrease in the urinary concentration of the urinary salts that prevent supersaturation of the crystallizing salts.(30)

Digitalis purpurea-Foxglove is a species of flowering plant in the genus *Digitalis*, belongs to the family Plantaginaceae. It contain Cardiac glycosides named digitoxin, digoxin and gitoxin. Its aqueous extract showed prominent diuretic and anti-urolithic activity as it is already well-known for its usefulness as a cardiac, diuretic, stimulant and tonic, it helps urination by improving the blood supply to the kidneys and helpful in removing obstructions within the kidneys may be due to its glycosides content.(23)

Orthosiphonstemineus-Cat whiskers is an herb which belongs to family Lamiaceae.It consist of monoterpenes and sesquiterpenes i.e.- β-caryophyllene, α-humulene, β-elemene, 1-octen-3-ol, β-bourbonene, β-pinene, caryophyllene oxide, camphene and limonene.It has been used for the treatment of kidney & bladder stone and urinary infection attributed to its diuretic, antiseptic &litholytic property. Its flavonoids were found to possess adenosine A_1 receptor binding activity which induce diuresis & sodium excretion (31)

Convolvulus arvensis- *C. arvensis* belongs to family Convolvulaceae. It has many therapeutic benefits such as its use in tribal area as the root, is cholagogue, diuretic, laxative and strongly purgative. Aerial parts of this plant showed the presence of various compounds such as saponins, terpinoids, steroids, tropane alkaloids (Pseudotropine, tropine, tropinone, meso-cuscohygrine, Hygrine, calystegine and atropine), flavonoids (Kaempferol, Quercetin and rutin), phenolic acids and different quantities of

essential elements.The leaf infusion of *C. arvensis*has shown significant urolithiolytic activity than that of the flower infusion due to its diuretic activity.[32]

***Raphanussativus*-** Radish is an edible root vegetable of the Brassicaceae family. It mainly contain glucosinolate, myrosinase, and isothiocyanate which are responsible for their sharp flavour.A significant decrease in the weight of stones was observed after treatment in animals which received aqueous extract of *Raphanussativus*. This extract showed an increase in the 24 h urine volume due to its diuretic effect.[33]

3} Antioxidant property:

Injury to the epithelial cells of the kidney in the presence of calcium is mediated by the overproduction of reactive oxygen species (ROS), produced mostly from mitochondria or nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The interaction between injured renal tubular epithelium and CaOxcrystals or oxalate ions is likely to play a critical role in the formation of urinary calculi.[34]

***Citrus sinensis*-**Sweet orange is the fruit of the citrus species in the family Rutaceae. Ithas a high antioxidant capacity due to the presence of citrate, vitamin C, vitamin E and flavonoids such as eriocitrin, hesperetin and limonoids. Vitamin E may prevent calcium oxalate crystal deposition in the kidney by preventing hyperoxaluria-induced peroxidative damage to the renal tubular membrane surface (lipid peroxidation), which in turn can prevent calcium oxalate crystal attachment and subsequent development of kidney stones.[35,36]

***Zingiberofficinalis*-** Zingeris a rhizome belongs to family zingiberaceae, that is widely used as culinary herb and herbal remedy for some common ailments.. It contains about 1-2% of volatile oil and 5-8% of resinous matter, starch and mucilage. Ginger has been reported to possess a potent anti-oxidant activity in vitro which reduces the oxidative stress in the body. Administration of its ethanolic extract to ethylene glycol rats prevented super saturation of calcium oxalate and thus decreased their deposition in renal tubules due to active compound present in the extract..[37]

Mimusopselengi*–Mimusopselengi* is a medium-sized evergreen tree commonly called maulsari belongs to family sapotaceae. Bark of M. elengi contains tannin, some caoutchouc, wax, coloringmatter, starch, ash forming inorganic salts,Saponin, which on hydrolysis yielded β-amyrin and bassic acid[18]the increased deposition of stone forming constituents in the kidneys of calculogenic rats were significantly ($P < 0.001$) lowered by curative and preventive treatment with alcohol extract of M. elengi. It was also observed that alcoholic extract of M. elengi produced significant ($P < 0.001$) decrease in MDA, and increased GSH, SOD, and CAT. Which confirm that *M. elengi* possess potent antiurolithiatic activity due to its antioxidant effect.[38]

Hordeum vulgare-Hordeum is a genus of annual and perennial plants in the grass family poaceae.It contain flavonoid i.e.-saponarin which on hydrolysis gives equilibrium mixture of saponaretin&vitexin, which is responsible for its antioxidant effect.Ethanolic extract of *Hordeumvulgare* seeds (EHV) significantly reduced the urinary excretion of the calcium, phosphate, uric acid, magnesium, urea, and oxalate and increased the excretion of citrate compared to EG control. It was also observed that the treatment with EHV produced significant decrease in lipid peroxidation, and increased levels of superoxide dismutase and catalase and concluded that urolithiatic effect is due to antioxidant activity.(39)

Punicagranatum-Pomegranate is a fruit-bearing deciduous shrub belongs to family Lythraceae.The administration of *punicagranatum*extract (chloroform & methanol) in EG induced urolithiatic rats resulted in removal of deposition of CaOx crystals into kidneys, improving renal histology and GFR. Antioxidants, polyphenols and alkaloid of PG is therapeutically effective for the treatment of calcium oxalate stones, exhibiting effects through a combination of antioxidantand anti-inflammatory action, which could be responsible for its antilithiatic activity.(40)

Cymbopogoncitratus-Lemongrass is a tropical plantof family Poaceae and itsoil has been evaluated for its antioxidant properties. Citral, a main constituent of lemongrass oil, significantly inhibited the formation of micronuclei induced by nickel when the antioxidant activity of citral was tested in vitro.*Cymbopogoncitratus*was antigenotoxic against gamma-rays in another study again suggesting free radical scavenging mechanism.This property may be used for treatment of urolithiasis.(20)

Citrus sinensis- *C. sinensis*belongs to family Rutaceae& containhesperidin which is a flavanone glycoside comprising the flavanone, hesperitin and the disaccharide rutinose.Hesperidin, an abundant bioflavonoid in citrus fruits, has been reported to possess antioxidant property. This property is responsible forantilithiasis activity of hesperidin a glycoside flavanone extracted from leaves peelof C.sinensis.(41)

Bergeniaciliata-*B. ciliata*, commonly known as Paashaanbhed in the Indian Systems of Medicine, is used as a tonic for treatingfevers, pulmonary infections, and hypoglycaemia,and has anti-inflammatory, antioxidant and antifungalproperties.The major chemical constituents reported from B. ciliata are gallic acid, bergenin (+)-afzelechin, 11-O-galloyl bergenin, paashaanolactone, b-sitosteroland b-Sitosterol-d-glucoside. A phenolic compound isolated from the leaves of B. ciliata was effective in dissolvingCaOx and calcium phosphate urinary stones and 70% methanolicextract from therhizomes of B. ciliata had a significantprotective effect on the histopathological changes in ananimal model of hyperoxaluria due to its antioxidant effect.(42)

Curcuma longa- Rutin and curcumin are the polyphenolic compounds present in turmeric, known to have antioxidant and anti-inflammatory activities.Supplementation of rutin and curcuminrestored elevated levels of calcium and oxalate in the urine and kidney sample near to normal and showed minimum tissue damage and less number of calcium oxalate deposits in kidney of animal treated with rutin and curcumin as compared to calculi-induced animal.This effect is mediated possibly through a lowering of urinary concentration of stone forming constituents, anti-inflammatory and antioxidant effects.[43]

AsphaltumPanjabinum-*AsphaltumPanjabinum* known as Shilajit has been a panacea in oriental medicine.Shilajit contains bio- assimiable glycine and glutamate as two of its constituents which helps in the synthesis of glutathione, which itself is a good antioxidant. Antioxidant effect of Shilajitseems to be of value in the prevention of oxidative stress induced initial stage of nidus formation in urolithiasis as well as for the prevention of recurrence of stone formation. Thus shilajit can be used as nutraceutical in such pathological states.[44]

Kigeliaafricana-*Sausage Tree* belongs to family Bignoniaceae and used in treatment of various diseases like rheumatism, snakebites, evil spirits, venereal diseases like syphilis including renal disorders. Flavonoid and saponincontents of fruit attributes antioxidant property to *kigelia Africana*. The aqueous and alcoholic extracts significantly decreased ($p < 0.001$) crystal size and increased calcium and oxalate concentration and also found that the aqueous extract of the fruits of plants *Kigeliaafricana* has shown more significant anti-lithiatic activity in dissolution of generated calcium oxalate crystals compared to alcoholic extract.[45]

4} Inhibition of oxalate synthesizing enzyme:

Aervalanata-*Aervalanata* belongs to family Amaranthaceae and contain flavonoids, alkaloids, steroids, polysaccharides, tannins, saponins etc.Administration of *A.lanata* aqueous suspension(2g/kg b.wt) to CaOxurolithic rat had reduced oxalate synthesizing enzyme(Glycolic acid oxidase & lactate dehydrogenase), diminished marker of crystal deposition in the kidney and confirmed that it can be used as curative agent in urolithiasis.[46]

Tribulusterrestris-The genus *Tribulus*, belonging to family Zygophyllaceae. Its various parts contain a variety of chemical constituents which are medicinally important, such as flavonoids, flavonol glycosides, steroidal saponins, and alkaloids. Glycolate oxidase (GOX) is one of the principal enzymes involved in the pathway of oxalate synthesis converting glycolate to glyoxylate by oxidation and finally to oxalate. The antiurolithic activity of TT is attributed to its GOX inhibition.[42]Quercetin and kaempherol, the active components of TT, were found to be non-competitive and competitive inhibitors of GOX, respectively.[47]

5} Mixed action:

***Centratherumanthelminticum*-**Bitter cumin belongs to family Asteraceae. It contain various secondary metabolite like- aliphatic fatty acids, flavones, saponins, steroids and glycosides. It is concluded that 28 days oral treatment with 70% methanolic extract of *C. anthelminticum* seeds has potential antiurolithiatic activity against ethylene glycol induced nephrolithiasis, mediated possibly through a combination of diuretic, antioxidant and hypermagnesuric effects.(8,48)

***Phyla nodiflora*-** It is a perenial herb from family Verbenaceae and contain flavone glycosides including lippiflorin A & B, nodiflorin A & B, nodifloritin A & B, alkaloid, essential oil, resin, B-sitosterol, sugar and diflavones. It is used as anodyne, cardiotonic, antibacterial, refrigerant & diuretic. Antiurolithiatic activity of this plant can be attributed to its ability to reduce supersaturation of urine with calculogenic ion, diuretic property & antioxidant potential.(21)

Mussaendaerythrophyla*-Mussaendaerythrophylla*, commonly known as Ashanti Blood belongs to rubiaceae family. Iridoids, flavonoids and triterpenes are the common chemical ingredients distributed in *Mussaenda*species, which are responsible for its antiurolithiatic effect. It was also observed the increased deposition of stone forming constituents in the kidneys of calculogenic rats were significantly lowered by curative and preventive treatment with chloroform extract (ClE) of *Mussaendaerythrophyla* root & produced significant In vitro antioxidant effect.(49)

***Citrus medica*-**Citron is a large fragrant citrus fruit which belongs to Rutaceae family.*Citrus medica*fruits are known to contain flavonoids, phenols, citric acid, essential oil, Limonene and y-terpinene. Among all of these constituents, flavanoids are reported for antiurolithiatic action. FFCM possess anti-lithiatic activity in experimentally induced urolithiatic model (Ethylene glycol model), that can be attributed to its diuretic action, decrease in promoters and increase in inhibitors level & antioxidant potential.(50)

***Stigma maydis* -**Corn silk is made from stigmas, the yellowish thread like strands from the female flower of maize of family Poaceae. It contain fatty acid 2.5%, volatile oil 0.12%, gum 3.8%, resin 2.7%, saponin 3.18%, alkaloids 0.05%, flavonoids, allantoin and moderate amount of zinc, potassium, calcium, phosphorus. The rational behind its use for the treatment of kidney stones is that it reduces irritation, increases urine secretion & in addition, it possesses excellent antioxidant capacity. It was found that the alcoholic extract antiurolithiaticactivityin dissolution of regenerated calcium oxalate crystals(51)

Tinosporacordifolia*-Tinosporacordifolia* from familyMenispermaceae has been claimed to possess antidepressant, antistress, learning and memory enhancing, antioxidant & diuretic effect. The ethanolic extract of *T. cordifolia* stem have inhibitoryeffect on CaOx crystallization thus may be beneficial in the

treatment of urolithiasis.Diuretic effects may also reduce stone development when total fluid intake and output increased, and such effects have been attributed to several herbal preparations.[52]

Trigonellafoenum-graecum- Fenugreek belongs to FamilyFabaceae. Its seeds have beenused by traditional herbalists for problems of kidney and malereproductive tract.Trigonelline (N-methylnicotinic acid, N-methyl betaine) is the major alkaloid phytoconstituent of fenugreek seeds act by suppression ofoxidative stress in kidney and reduction in renal cell apoptosis and fibrosis. Increased diuresis, antioxidant activity and lowering of urinary concentrations of stone forming constituents are suggested mechanism for anti-urolithiatic effects of fenugreek seeds.[53]

Conclusion

In conclusion,considering all available evidences present review suggested that antiurolithiatic drugs has multiple mechanism of action including-Alteration in physiological pH,Diuretic activity, Antioxidant activity, Inhibition of oxalate synthesizing enzyme and some drug often shows more than one mechanism of action. Therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. In this review article, an attempt has been made to compile the reported mechanism and phytochemical constituent of different herbal drug which may be responsible for its therapeutic and traditional use in urolithiasis. Although these herbal medicine are popular in folk culture but rational behind safety & efficacy of these herbal medicine is not well established. Precise understanding of mechanism of action of these herbal medicine has great importance in development of safe & effective antiurolithiatic drug and it may be useful to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure urolithiasiswithout any toxic effects and also to reduce chances of stone recurrence. It provide the basis for future research on the application of transitional medicinal plants.

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